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31. (Previously added) The ~~vaccine~~ composition of Claim 1, wherein said recombinant immunoglobulin molecules are conjugated to a foreign carrier protein.

32. (Previously added) The ~~vaccine~~ composition of Claim 31, wherein said foreign carrier protein comprises keyhole limpet hemocyanin.

REMARKS

Applicant notes with appreciation that the Examiner's objection under 35 U.S.C. 132 to the amendment filed on 4/29/02 has been withdrawn, and further that the amendment mailed received 1/6/03 has been entered into the record.

The Examiner states that Claims 1, 3-6 and 25-**30** are currently pending in this case (page 2, under "Detailed Action"). This is incorrect, as Claims 31 and 32 are also pending. Claims 1-24 were originally filed in a parent case, and were subject to restriction; Claims 1-6 were elected for prosecution in this divisional case. Claims 25-32 were subsequently added, and Claim 2 was canceled in a Response to an Office Action dated December 19, 2000. No additional claims have been canceled. Thus, Claims 1, 3-6 and 25-**32** are currently at issue in the present application.

The Examiner has rejected these Claims in an Office Action mailed April 9, 2003. For clarity, the rejections at issue are set forth by number in the order they are addressed herein:

(1) Claims 1, 3-6, and 25-32 are rejected under 35 U.S.C. § 112, paragraph one, as allegedly not being enabled.

(2) Claims 1, 3-6 and 25-32 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Tao et al. (362 Nature 755-758; hereinafter Tao), Stevenson et al. (in DNA Vaccines - A New Era in Vaccinology, Volume 72 Annals of the New York Academy of Sciences 212-226; hereinafter Stevenson), and de The (19 Blood Cells 667-675).

(1) 35 U.S.C. § 112, paragraph one rejections:

The Examiner has rejected Claims 1, 3-6, and 25-32 under 35 U.S.C. § 112, paragraph one, as allegedly not being enabled. In particular, the Examiner alleges that the use of the

term "vaccine" is not supported because applicants have not shown by challenge studies that vaccination prevent reoccurrence of the cancer. For reasons already of record in this case, Applicant asserts that the Examiner is applying a definition of the term "vaccine" that is contrary to the usage known to practitioners in this field.

However, without acquiescing to Examiner's arguments, Applicant proposes amending independent Claims 1, 25, 28, 29 and 30 to recite instead a multivalent "composition for active idiotype immunotherapy". Dependent Claims 3-6, 31 and 32 have been amended to delete the word "vaccine" and to refer to the compositions of the claims from which they depend.

Support for the term "active idiotype immunotherapy" is found , e.g., at first sentence of Example 10, on page 88, where it is disclosed that active immunotherapy for B-cell lymphoma involves production of a vaccine comprising the immunoglobulin idiotype corresponding to an antibody on the surface of the B-cell tumor.

(2) 35 U.S.C. § 103(a) rejections

a. de The does not teach quasi-clonal B-cell lymphomas>

Without acquiescing to Examiner's arguments, Claims 1, 25, and 28-30, and thus the claims depending therefrom, have been amended to recite that the claimed compositions are derived from "quasi-clonal" B-cell lymphoma cells. Support for this term is found, e.g., at page 52, lines 18-26. As described in the specification, the term "quasi-clonal" refers to clonal tumors wherein different idiotypes may be present due to the process of somatic mutation. The process of somatic mutation leads to the accumulation of point mutations within the heavy and light chain V region genes that are expressed in the tumor. These tumors are clonal on the level of DNA rearrangement (i.e., the rearranged allele) but are not identical and thus are quasi-clonal at the level of the nucleotide and amino acid sequences derived from the somatically mutated rearranged V region gene.

Such limited variation within the tumor is distinct from the polyclonal tumors that can arise in immunocompromised patients, as discussed by de The, where multiple transformation events give rise to tumors that are polyclonal at the level of allelic rearrangement.

The present invention is directed toward multivalent preparations for immunotherapy that comprise a mixture of immunoglobulin V region sequences derived from quasi-clonal

tumor cells that reflect the full complement of variants in any particular patient's quasi-clonal tumor.

b. Tao does not teach multivalent quasi-clonal B-cell lymphomas, or immunotherapy directed to them>

Tao teaches cytokine-linked idiotype immunotherapies but does not teach multivalent preparations for immunotherapy. Tao does not disclose quasi-clonal B-cell lymphomas.

c. Stevenson teaches **away** from multivalent immunotherapies for quasi-clonal B-cell lymphomas.

Stevenson does address the issue of somatic mutation in follicular B cell lymphomas, as raised by the Applicant in the present application. However, instead of teaching the usefulness of producing a multivalent immunotherapy preparation, Stevenson argues away from such preparations:

> For certain B cell tumors, such as follicular lymphoma, which may continue to be exposed to the somatic mutation mechanism following neoplastic transformation, a degree of intraclonal mutational heterogeneity is know to occur, and this was observed in our patients. However, we do not consider that this presents a problem for vaccination for two reasons: first, there was usually a predominant sequence and second, changes in most or all of the idiotypic determinants would be necessary to allow escape of tumor cells from a polyclonal immune attack. For vaccine design, we have chosen to assemble the predominant tumor-related sequence . . ."

Stevenson et al., p213.

Thus, one skilled in the art, even appreciating the intraclonal heterogeneity that may occur in a B cell lymphoma, nonetheless teaches away from the multivalent preparations of the present invention. As noted in the present application at Page 59, line 4, the fact that somatic variants exist within B-cell tumors has implications for treatment by immunotherapy. Treatment of B-cell lymphomas with monoclonal (i.e., monovalent) anti-idiotype antibodies has been shown to produce an initial response but it has also been shown that idiotype variant tumor cells (idiotype negative) later emerged at the original tumor site. It is thought that these idiotype variant cells were present before treatment and that they were allowed to proliferate after the selective removal of the idiotype positive cells (references at page 53, lines 2-4 of the present application).

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The prior art vaccines have been monovalent and thus they do not represent the full complexity of the immunoglobulins expressed by tumors that contain somatic variants. The multivalent compositions for active idiotype immunotherapy of the present invention, comprising a collection of recombinant variable regions of immunoglobulin molecules that are derived from quasi-clonal B-cell lymphoma cells of a single patient and that differ by at least one idiotope, thus provide an active immunotherapy that is more representative of the multiple variants of the immunoglobulins present in the patients quasi-clonal tumor and represent a significant advantage over the prior art's use of monovalent idiotype protein vaccines.

The only reference to address the quasi-clonal nature of the B-cell lymphomas treated by the therapies of the present invention, Stevenson, teaches away from the production of multivalent preparations. This teaching away is not overcome by either Tao or de The. Thus, none of these references, either alone or in combination, teach or suggest the multivalent compositions for active idiotype immunotherapy of the present invention.

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